Respiratory Medicine (2014) 108, 1134–1140

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Exercise programme in patients with cystic fibrosis: A randomized controlled trial

Paula Maria Eidt Rovedder [a,*], Josani Flores [b], Bruna Ziegler [b], Fernanda Casarotto [c], Patrícia Jaques [b], Sergio Saldanha Menna Barreto [b], Paulo de Tarso Roth Dalcin [d]

[a] *Faculdade de Fisioterapia, Universidade Federal do Rio Grande do Sul (UFRGS), Brazil*
[b] *UFRGS, Brazil*
[c] *Faculdade de Medicina, UFRGS, Brazil*
[d] *Serviço de Pneumologia, HCPA, Faculdade de Medicina, UFRGS, Brazil*

Received 9 April 2013; accepted 15 April 2014
Available online 26 June 2014

KEYWORDS
Cystic fibrosis;
Home exercise programme;
Aerobic training;
Muscle strength training

Summary
Objectives: Assess the effects of a home exercise programme, based on aerobic training and muscle strength training, in patients with cystic fibrosis (CF), for a period of 3 months.
Methods: Randomised controlled clinical experiment, with an analysis of intention to treat including clinically stable patients with CF and of age $\geq$ 16. Assessments include: a 6 min walk test (6 MWT), one-repetition maximum strength test (1 RM), spirometry and quality of life questionnaires. The patients randomised for the exercise group exercise group followed a home exercise protocol, supervised by telephone, while the control group maintained their usual activities.
Results: 41 Patients were included, 22 in the control group and 19 in the exercise group. The exercise group presented a significant increase in muscle strength in upper limbs (UULL) on the 1 RM test. There was no significant difference between groups on the scores for general quality of life and specifically for CF and in the distance walked on the 6 MWT.
Conclusion: The study demonstrated that a home exercise programme had positive effects in adult patients with CF, including gain in muscle strength in UULL. No increase in tolerance to exercise was shown and improvement in the quality of life of the patients who received intervention.

* Corresponding author. Rua Domingos Crescêncio 185/502CEP: 90650-090, Brazil. Tel.: +55 51 32171757.
E-mail addresses: paula.rovedder@metodistadosul.edu.br, larove_@hotmail.com (P.T.R. Dalcin).

http://dx.doi.org/10.1016/j.rmed.2014.04.022
0954-6111/

Introduction

Cystic fibrosis (CF) is a hereditary disease most common in the white population [1]. The clinical expression of the disease is very varied in general, showing multi-systemic involvement, characterised by intestinal motility, male infertility and high concentrations of electrolytes in sweat. However, pulmonary impairment is the main determinant of morbidity and mortality related to the disease [2,3].

Patients with CF frequently present a progressive limitation to physical exercise and reduction of their daily life activities [4–7]. However, when submitted to physical activity programmes, these patients present an increase in tolerance to exercise, improvement in cardiorespiratory function, in respiratory muscle endurance and in immunological function [8–12].

Training with aerobic exercise has been associated with improvement in the prognostic of patients with CF [11]. The best results were reached with supervised training programmes [5–14].

An important alternative to be considered in this population of patients would be to institute a home exercise programme supervised by the health care team. These home programmes correspond to a proposal closer to the reality of this population, that is, patients with varying seriousness of the disease, residents in different locations, with no possibility of carrying out the exercise protocol with weekly presential intervention at the centre, could benefit from this intervention. However, evidence of benefit from this approach is still precarious [16–18].

The aim of this study was to assess the effects of a home exercise programme, based on aerobic training and muscle strength training, in adult patients with CF, for a period of 3 months.

Methods

The study comprised a prospective, randomised controlled clinical trial, with an intention to treat analysis, and consecutively included patients attended through the Programme for Adults with CF at the Porto Alegre Clinical Hospital (HCPA) where volunteers stepped up. The protocol was approved by the Ethics Committee at the HCPA (07164) and a free informed term of consent was signed by each patient.

The study included patients diagnosed with CF in accordance with the criteria of the consensus [1], 16 years of age or older, with at least 30 days of clinical respiratory disease stability. Patients who refused to take part in the study, pregnant ladies, individuals with heart disease, orthopaedic or traumatological problems, were excluded.

The assessment of the study included: a 6 min walk test (6 MWT), muscle strength test, spirometry and quality of life questionnaire. These assessments were carried out at two moments: at the start and after three months of conducting the trials. These assessments were carried out by one of the researchers who was blind to the randomisation and the intervention, throughout the study. This researcher was responsible for controlling the filing of all the test results and transference of the test results to a database, numbered, with no nominal identification to keep the process a blind study for all the other authors.

The 6 MWT was carried out in accordance with the guidelines of the *American Thoracic Society* [19]. The total distance walked in 6 min was recorded in meters and in the % of the predicted distance [20]. The peripheral oxygen saturation (SpO_2) were measured by means of a pulse oxymeter (NPB-40; Nellcor Puritan Bennett; Pleasanton, CA, EUA). The perception of the sensation of dyspnoea and fatigue of the lower limbs were recorded according to the Borg scale [21].

Measuring muscle strength consisted of a one-repetition maximum strength test (1 RM). The 1 RM test is defined as the maximum weight lifted once during the performance of a standardised weight lifting exercise. The 1 RM test involves two muscle groups: elbow flexors and knee extensors [22].

Spirometry was performed by means of a spirometer (MasterScreen, v4.31, Jaeger, Würzburg, Germany). Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and a FEV_1/FVC ratio were recorded. The test was carried out in accordance with the reproducibility and acceptability criteria of the Brazilian Society of Pneumology and Tisiology [23].

The quality of life was assessed by the questionnaire specifically for CF [24] (CFQ — Cystic Fibrosis Questionnaire), and by a questionnaire of general scope *Medical Outcomes Study-36 Item Short-Form Health Survey* (SF-36), also valid for the Portuguese language [25].

After the first assessment, the patients were submitted to the process of randomisation. This process uses a computer programme (*Random Allocation Software* version 1.0, developed by M. Saghaei, MD., *Department of Anaesthesia, University of Medical Sciences, Isfahan, Iran*), in blocks of six patients. The patients were allocated to two groups: an exercise group (G1) and a control group (G2).

The patients randomised for G2 continued receiving standard follow-up from the adult programme physiotherapist, every two months. In this follow-up the patients were advised on frequency and techniques of respiratory physiotherapy and on the practice of physical exercise.

The patients randomised for G1, as well as follow-up from the adult programme physiotherapist, they were advised, to do a specific home exercise programme.

After randomisation, the first meeting was booked for providing the training instructions, providing available material for the exercise and the patient was acquainted with its use. These orientations were reinforced at each return visit to the outpatient department and through weekly telephone contact during the three month period.

The exercise protocol was based on aerobic training and muscle strength training to be performed daily. The patients received printed guidance material and practical demonstration by the researcher, on the appropriate performance of each physical exercise recommended by the protocol.

For muscle strength training, the patients received practical guidance and printed copies of the exercise protocol for strengthening muscles. The patients were advised to perform the protocol daily.

The main outcome of the study was defined as the variation on the score for quality of life. The secondary

outcomes were defined as the variation in distance walked on the 6 MWT and the variation of maximum load reached on the 1 RM test.

The estimation of the calculation for sample size was done using the quality of life variable (SF-36). To reach a difference of 5 points between two groups for the quality of life questionnaire, with standard deviation of 5, with a power of 90% and level of significance 0.05, 23 patients would be needed in each group [24].

Statistical analysis

The data were expressed in number of cases (proportion), average ± SD or median (interquartile range). The comparisons between the categorical variables were done by the chi-square test with adjusted standardised residuals, applying Yates correction or the Fisher exact test when indicated. The *t* test for independent samples was used for the comparisons of the continuous variables with normal distribution between two groups. The Mann–Whitney *U* Test was used for the comparison of ordinal variables or continuous variables with no normal distribution.

Imputation of missing data was used for two patients who did not participate in the second assessment of the exercise programme, because they were submitted to a lung transplant during the follow-up process. The *Statistical Package for the Social Sciences*, version 18.0(SPSS Inc., Chicago, IL, USA) was used for the imputation of data, and from the original example 5 database were generated with values estimated for these two patients in the second moment of the study. The values of these 5 database were added for the generation of a single database with an average of values for these database. This single database was used as reference for the whole statistical analysis of this study [26].

The data was analysed using the SPSS programme version18.0. The level of statistical significance was established at $p < 0.05$. All the statistical tests used were bicaudal.

Results

In the period between April, 2008 and March 2011, 60 patients were invited for inclusion in the study. Of these, 19 refused to participate for the following reasons: 6 argued that they already did regular physical activity, 5 did not have time for doing exercise, 3 did not like to exercise at home, 3 did not want to do any physical activity, 1 did not like to participate in clinical trials, 1 was trying to get pregnant. Therefore, 41 patients were included in the study. Fig. 1 presents flow diagram for the study.

Twenty-seven of the patients studied (65.9%) were female. The average age was 24.73 ± 7.57 years old, the average FEV_1 was 57.95 ± 25.15% of the predicted and all the patients were Caucasian.

Table 1 shows the comparison of general characteristics between the exercise and control groups. Nineteen patients were randomised for the exercise group and 22 for the control group. The exercise group presented a BMI significantly lower than the control group ($p = 0.011$). There was no significant difference between the two groups for other characteristics.

Table 2 presents the comparison of dominions of quality of life in cystic fibrosis and SF-36 between the intervention

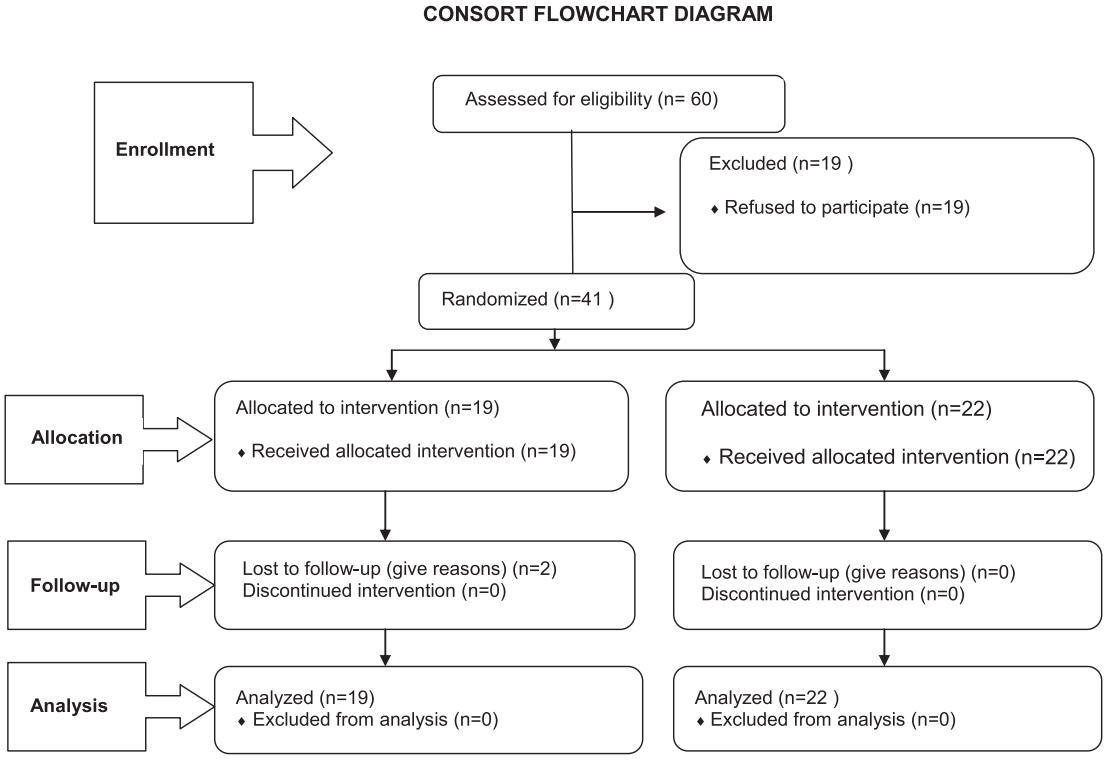

Figure 1 Flow diagram for the study.

Table 1 Comparison of general characteristics between intervention and control groups.

Variables	Exercise (n = 19)	Control (n = 22)	p
Age[a] (years)	23.8 ± 8.3	25.4 ± 6.9	0.407
Sex[b] (male/female)	7/12	7/15	0.804
BMI[a] (Kg/m^2)	19.8 ± 2.4	21.4 ± 2.1	0.011
FEV_1[a] (% predicted)	58.3 ± 27.6	57.6 ± 22.7	0.709
FVC[a] (% predicted)	71.6 ± 2.9	71.5 ± 19.0	0.984
Physical activity[c] (% of yes)	31.6%	31.8%	0.825
Distance in 6 MWT[a] (metres)	540.2 ± 79.5	549.0 ± 36.8	0.643
SpO_2 at rest[a] (%)	95.8 ± 2.3	96.8 ± 2.0	0.165

Chi-square test for categorical variables; t test for independent samples for continuous variables with normal distribution.
[a] Values expressed in average ± SD.
[b] Values expressed in number of cases.
[c] Values expressed in %. BMI = body mass index; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; 6 MWT = 6 min walk test; SpO_2 = peripheral oxygen saturation.

and control groups at baseline. There were no statistically significant differences observed in the assessment of the different dominions of quality of life for the two questionnaires used [24,25].

Table 2 Comparison of dominions of quality of life in cystic fibrosis and SF-36 between exercise and control groups at baseline.

Dominions	Exercise (n = 19)	Control (n = 22)	p
QoLQ — physical	58 (45/87)	64 (44/81)	1.000
QoLQ — body image	77 (55/77)	77 (66/88)	0.211
QoLQ — digestion	88 (88/100)	88 (74/100)	0.187
QoLQ — respiratory	55 (50/72)	55 (38/61)	0.311
QoLQ — emotional	86 (66/93)	73 (46/86)	0.060
QoLQ — social	61 (44/72)	63 (48/77)	0.572
QoLQ — food	88 (77/100)	100 (77/100)	0.843
QoLQ — treatment	55 (44/66)	55 (38/66)	1.000
QoLQ — vitality	66 (58/75)	62 (41/75)	0.348
QoLQ — health	55 (33/77)	44 (33/77)	0.968
QoLQ — weight	33 (33/66)	66 (33/100)	0.237
QoLQ — social role	83 (58/91)	83 (64/91)	0.749
SF-36 — functional capacity	75 (70/90)	80 (63/95)	0.645
SF-36 — physical aspects	75 (25/100)	87 (50/100)	0.280
SF-36 — pain	72 (51/84)	61 (51/88)	0.691
SF-36 — general health	52 (47/57)	52 (35/57)	0.863
SF-36 — vitality	65 (50/80)	57 (38/66)	0.192
SF-36 — social aspects	62 (50/87)	75 (59/100)	0.611
SF-36 — emotional aspects	66 (33/100)	66 (33/100)	0.956
SF-36 — mental health	76 (56/84)	70 (55/84)	0.732

Values expressed in median (percentile 25/percentile 75).
QoLQ = quality of life questionnaire in cystic fibrosis for patients of age ≥ 14 years. SF-36 = generic questionnaire on quality of life *Medical Outcomes Study 36-item Short-Form Health Survey*. Mann—Whitney *U* Test.

Table 3 shows the comparison of differences between exercise and control groups after 3 months of follow-up. The exercise group presented a significant increase in muscle strength in upper limbs (UULL) compared with the control group on the 1 RM test (p = 0.011 for the left upper limb and p = 0.029 for the right upper limb). There was no significant difference in the variables related to the 6 MWT.

Table 4 presents the comparison of differences in the dominions of quality of life in cystic fibrosis and SF-36 between exercise and control groups after three months of study. No statistically significant differences were observed between different dominions of quality of life for the two questionnaires used.

Discussion

This randomised and controlled clinical trial showed that, in adult patients with CF, a home exercise programme, based on aerobic training and muscle strength training, coupled with supervision by telephone, had a positive impact on the exercise group after the 3 months of conducting the trial, contributing to the significant increase of muscle strength in UULL of this group of patients, although, no effect on the scores of the general quality of life have been observed nor specifically for CF nor on the distance walked on the 6 MWT.

Table 3 Comparison of differences between intervention and control groups after 3 months of follow-up.

Variables	Exercise (n = 19)	Control (n = 22)	p
ΔFEV_1 (% predicted)	−6.0 ± 16.1	−2.0 ± 7.3	0.306
ΔFVC (% predicted)	−6.8 ± 17.7	−3.5 ± 8.3	0.445
6 MWT			
ΔDistance (meters)	−7.0 ± 39.8	−6.2 ± 37.5	0.947
ΔDistance (% predicted)	−1.2 ± 5.9	−3.1 ± 9.9	0.478
ΔSpO_2 at rest (%)	−0.1 ± 1.3	−1.0 ± 2.1	0.097
ΔSpO_2 at the end of 6 MWT (%)	1.3 ± 5.4	−1.3 ± 2.9	0.052
ΔRR at the end of 6 MWT (irpm)	−0.3 ± 5.0	0.7 ± 9.5	0.652
ΔHR at the end of 6 MWT (bpm)	−0.4 ± 20.7	−5.1 ± 24.6	0.510
ΔBorg dyspnoea at rest	0.1 ± 0.4	0.1 ± 0.8	0.985
ΔBorg dyspnoea at the end of 6 MWT	−0.4 ± 2.1	−0.3 ± 1.8	0.863
ΔBorg fatigue at rest	0.02 ± 0.8	0.0 ± 0.9	0.944
ΔBorg fatigue at the end of 6 MWT	−0.9 ± 2.6	−0.3 ± 1.2	0.267
Δ1 RM in LUL	1.2 ± 2.2	−0.2 ± 1.0	0.011
Δ1 RM in RUL	1.0 ± 1.7	0.0 ± 0.9	0.029
Δ1 RM in LLL	2.4 ± 1.9	0.8 ± 2.8	0.053
Δ1 RM in RLL	2.1 ± 2.0	1.0 ± 3.2	0.199

Values expressed in average ± SD. Δ = difference.
FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; 6 MWT = 6 min walk test; SpO_2 = peripheral oxygen saturation. RR = respiratory rate; HR = heart rate; 1 RM = one-repetition maximum strength test; LUL = left upper limb; RUL = right upper limb; LLL = left lower limb; RLL = right lower limb. t test for independent samples.

Table 4 Comparison of differences dos dominions of quality of life in cystic fibrosis and SF-36 between intervention and control groups.

Dominions	Exercise (n = 19)	Control (n = 22)	p
ΔQoLQ — physical	6.1 ± 17.50 (−4/8)	2.4 ± 17.50 (−10/13)	0.742
ΔQoLQ — body image	3.3 ± 17.20 (−11/22)	3.0 ± 22.20 (−2/11)	0.915
ΔQoLQ — digestive	−1.0 ± 9.00 (−4/0)	−0.5 ± 11.10 (0/0)	0.953
ΔQoLQ — respiratory	3.8 ± 10.60 (0/11)	−4.7 ± 13.40 (−1/7)	0.925
ΔQoLQ — emotional	1.2 ± 13.00 (−6/6)	−4.3 ± 17.80 (−13/6)	0.458
ΔQoLQ — social	−1.1 ± 18.50 (−11/5)	−1.7 ± 16.40 (−5/11)	0.822
ΔQoLQ — food	−0.3 ± 16.80 (−11/6)	−2.0 ± 15.10 (−11/0)	0.913
ΔQoLQ — treatment	−2.0 ± 15.50 (−11/0)	−2.5 ± 21.30 (−11/11)	0.850
ΔQoLQ — vitality	−1.2 ± 21.00 (−16/8)	2.6 ± 16.50 (−8/10)	0.579
ΔQoLQ — health	1.7 ± 22.00 (−11/16)	−3.0 ± 12.40 (−11/0)	0.382
ΔQoLQ — weight	4.6 ± 33.90 (0/33)	12.1 ± 24.20 (0/11)	0.410
ΔQoLQ — social role	0.8 ± 15.70 (−8/8)	1.8 ± 11.40 (−2/0)	0.935
ΔSF-36 — functional capacity	2.0 ± 18.10 (−10/15)	2.0 ± 22.40 (−11/10)	0.916
ΔSF-36 — physical aspects	11.8 ± 49.50 (−25/50)	6.8 ± 37.90 (−6/31)	0.705
ΔSF-36 — pain	−7.2 ± 29.2−10 (−28/11)	8.0 ± 19.90.5 (0/17)	0.100
ΔSF-36 — general health	3.7 ± 14.15 (−5/10)	−3.5 ± 15.4−2.5 (−11/5)	0.197
ΔSF-36 — vitality	1.2 ± 21.65 (−15/20)	7.5 ± 16.15 (−1/21)	0.416
ΔSF-36 — social aspects	15.2 ± 38.70 (0/33)	21.2 ± 43.00 (0/66)	0.989
ΔSF-36 — emotional aspects	4.7 ± 25.80 (−12/37)	4.5 ± 27.60 (−12/25)	0.914
ΔSF-36 — mental health	−0.8 ± 18.30 (−12/12)	0.9 ± 16.82 (−9/13)	0.752

Values expressed in median (percentile 25/percentile 75).
Δ = Difference. QoLQ = quality of life questionnaire in cystic fibrosis for patients of age ≥ 14 years. SF-36 = generic questionnaire on quality of life *Medical Outcomes Study 36-item Short-Form Health Survey*.
Mann—Whitney *U* Test.

Previous studies [14,27,28] which assessed strength training in patients with CF showed several benefits including an increase in muscle mass, muscle strength, body weight and a decrease in residual volume, attributing greatest flexibility and thoracic mobility. However, many of these studies present methodological limitations. Most of them are non-controlled studies, of small sample size, and a short period of intervention and also non-randomised. Orenstein et al. [15] studied 67 patients with CF and age between 8 and 18. The patients were randomised for two groups, the aerobic training group and the strength training group for the UULL. It was a guided home programme; the patients were reassessed after 6 months and at the end of a year. It was concluded that both sets of training increased muscle strength in UULL and improved the physical tolerance of patients with CF. According to some authors, the importance of an increase in muscle strength in patients with CF is directly related to an improvement in tolerance to exercise in these patients [11,15].

The fact that this study does not show any gain in muscle strength lower limbs (LLLL) may be explained by the difference size of the muscle groups exercised, that is, the UULL muscle groups are shorter than in the LLLL which enables the faster gain of trophism in these muscle fibres. This fact may contribute to the increase in more efficient muscle strength in UULL. Apart from this, the length of time the study was conducted may have been too short to show the same effect in training in both muscle groups [22].

However, it is noteworthy that, in this study, there was no improvement in the aerobic condition of the patients ($p > 0.05$). A possible explication for this fact could be that in many of the patients the combination of previous illness and lack of physical activity has contributed to the low tolerance to exercise and limited the gain in fitness [5,14]. Some patients with initial low physical fitness and poor tolerance to exercise are limited because they are badly trained and, accordingly, show great potential for improvement, but perhaps need a longer period of training than the three months of the study. On the other hand, patients with a more advanced illness, precarious pulmonary function and loss of peripheral skeletal muscle mass have a lower potential for improvement and gaining aerobic fitness.

The incremental shuttle walking test (ISWT) is widely used in patients with chronic respiratory diseases and proves to be more sensitive than the 6 MWT to detect early functional capacity of patients change, since the SWT requires more physical effort compared to the 6 MWT is a test that depends on the patient's wishes. Perhaps one of the hypotheses for the group of patients randomized to the intervention have not shown an increase in aerobic capacity, can be explained by the 6 MWT not be so sensitive to this population [29]. The ISWT can be considered a valid and reliable test to assess maximal exercise capacity in individuals with chronic respiratory diseases [29].

Furthermore, patients had moderate lung function decline and this favoured for them to complete the 6 MWT with ease [29]. A recent study [11], investigated the prevalence of muscle weakness and its relation to the tolerance to exercise in adult patients with CF. Fifty-six percent of the patients with CF presented muscle weakness in the quadriceps muscle and 75% presented distance walked on the 6 MWT lower than normal. Adult patients with CF

present a reduction in peripheral muscle strength and in tolerance to exercise and that the lack of physical activity significantly contributes to these alterations.

The quality of life, assessed through the two questionnaires [24,25], presented no modifications while following the study ($p > 0.05$). Hebestreit et al. [30] determined the effects of a supervised controlled training programme in patients with CF and of age between 12 and 40 years old. The intervention promoted positive effects on the consumption of VO_2max, the FVC% predicted and the quality of life of the patients with CF. The improvement in the quality of life of patients who took regular physical exercise seemed to be related to the long term training programmes, with good adherence and adaptation to the specific needs and preferences of each individual.

Two patients were submitted to a lung transplant during the follow-up period of the study. In these cases imputations of missing data were used as a method of dealing with the lack of assessment which should have been carried out in the second phase of the study [26]. The study rigorously followed the methods established by the clinical trials for intention to treat.

The present study shows some limitations. The fact of not having used the measurement of VO_2max consumption obtained from the cardiopulmonary force test as a measure for the outcome may have influenced the sensitivity for identifying variations in the aerobic condition of the patients studied. Another possible limitation was the length of time the study was conducted for, stipulated as three months, which may have been insufficient to show any significant impact on physical condition and in the quality of life of these individuals. Apart from this, the refusal of many of the patients to participate in the study, may have created a bias on excluding patients unaccustomed to exercise and passive to the potential benefit or this therapeutic approach.

The contribution of the study is in the way the practise of physical exercise is administered in the patient's home, supervised at a distance, as a way of facilitating and broadening access to this therapeutic recommendation, even though the benefit has been of a small magnitude.

In conclusion, the study demonstrated that a home exercise programme in adult patients with CF, during the three months, including aerobic and muscle strength training, no improvement in the quality of life of the patients who received the intervention. The secondary outcome of the study was to gain muscular strength in the upper limbs in patients randomized to the intervention.

Funding

The present study has received financial support from the Porto Alegre Clinical Hospital Research Incentive Fund (FIPE-HCPA).

References

[1] Yankaskas JR, Marshall BC, Sufian B, et al. Cystic fibrosis adult care: consensus conference report. Chest 2004;125(Suppl. 1): 1S—39S.
[2] Rosenstein BJ. What is a cystic fibrosis diagnosis? Clin Chest Med 1998;19(3):423—41.
[3] Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. J Pediatr 1998;132(4):589—95.
[4] Pinet C, Cassart M, Scillia P, et al. Function and bulk of respiratory and limb muscles in patients with cystic fibrosis. Am J Respir Crit Care Med 2003;168(8):989—94.
[5] Blau H, Mussaffi-Georgy H, Fink G, et al. Effects of an intensive 4-week summer camp on cystic fibrosis: pulmonary function, exercise tolerance, and nutrition. Chest 2002;121(4):1117—22.
[6] Barry PJ, Waterhouse DF, Reilly CM, et al. Androgens, exercise capacity, and muscle function in cystic fibrosis. Chest 2008; 134(6):1258—64.
[7] Barry SC, Gallagher CG. Corticosteroids and skeletal muscle function in cystic fibrosis. J Appl Physiol 2003;95(4):1379—84.
[8] Gulmans V, van der Laag J, Wattimena D, et al. Insulin-like growth factors and leucine kinetics during exercise training in children with cystic fibrosis. J Pediatr Gastroenterol Nutr 2001;32(1):76—81.
[9] Hebestreit A, Kersting U, Basler B, et al. Exercise inhibits epithelial sodium channels in patients with cystic fibrosis. Am J Respir Crit Care Med 2001;164(3):443—6.
[10] Schneiderman-Walker J, Pollock SL, Corey M, et al. A randomized controlled trial of a 3-year home exercise program in cystic fibrosis. J Pediatr 2000;136(3):304—10.
[11] Troosters T, Langer D, Vrijsen B, et al. Skeletal muscle weakness, exercise tolerance and physical activity in adults with cystic fibrosis. Eur Respir J 2009;33(1):99—106.
[12] Van DN. Exercise programs for children with cystic fibrosis: a systematic review of randomized controlled trials. Disabil Rehabil 2010;32(1):41—9.
[13] de JW, Grevink RG, Roorda RJ, et al. Effect of a home exercise training program in patients with cystic fibrosis. Chest 1994; 105(2):463—8.
[14] Orenstein DM, Franklin BA, Doershuk CF, et al. Exercise conditioning and cardiopulmonary fitness in cystic fibrosis. The effects of a three-month supervised running program. Chest 1981;80(4):392—8.
[15] Orenstein DM, Hovell MF, Mulvihill M, et al. Strength vs aerobic training in children with cystic fibrosis: a randomized controlled trial. Chest 2004;126(4):1204—14.
[16] Nixon PA, Orenstein DM, Kelsey SF, et al. The prognostic value of exercise testing in patients with cystic fibrosis. N Engl J Med 1992;327(25):1785—8.
[17] Orenstein DM. Exercise testing in cystic fibrosis. Pediatr Pulmonol 1998;25(4):223—5.
[18] Prasad SA, Cerny FJ. Factors that influence adherence to exercise and their effectiveness: application to cystic fibrosis. Pediatr Pulmonol 2002;34(1):66—72.
[19] ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166(1):111—7.
[20] Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 1998;158(5 Pt 1):1384—7.
[21] Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14(5):377—81.
[22] ACSM'S. Guidelines for exercise testing and prescription. 6 ed. USA: Lippincott, Williams &Wilkins; 2000.
[23] Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26(2):319—38.
[24] Quittner AL, Sweeny S, Watrous M, Munzenberger P, Bearss K, Nitza AG, et al. Translation and linguistic validation of a disease-specific quality of life measure for cystic fibrosis. J Pediatr Psychol 2000;25:403—14.
[25] Ciconelli R, Ferraz MB, Santos W, et al. Brazilian-Portuguese version of the SF-36. A reliable and valid quality of life outcome measure. Rev Bras Reumatol 1999:143—50.
[26] Marshall A, Altman DG, Holder RL, et al. Combining estimates of interest in prognostic modelling studies after multiple

imputation: current practice and guidelines. BMC Med Res Methodol 2009;9:57.
[27] Gulmans VA, de MK, Brackel HJ, et al. Outpatient exercise training in children with cystic fibrosis: physiological effects, perceived competence, and acceptability. Pediatr Pulmonol 1999;28(1):39—46.
[28] Strauss GD, Osher A, Wang CI, et al. Variable weight training in cystic fibrosis. Chest 1987;92(2):273—6.
[29] Parreira VF, Janaudis-Ferreira T, Evans RA, et al. Measurement properties of the incremental shuttle walk test: a systematic review. Chest 2014;145(6):1357—69. http://dx.doi.org/10.1378/chest.13-2071.
[30] Hebestreit H, Kieser S, Junge S, et al. Long-term effects of a partially supervised conditioning programme in cystic fibrosis. Eur Respir J 2010;35(3):578—83.